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Review

Polyphenols and their potential role to fight viral diseases: An overview

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ABSTRACT

Fruits, vegetables, spices, and herbs are a potential source of phenolic acids and polyphenols. These compounds are known as natural by-products or secondary metabolites of plants, which are present in the daily diet and provide important benefits to the human body such as antioxidant, anti-inflammatory, anticancer, anti-allergic, antihypertensive and antiviral properties, among others. Plentiful evidence has been provided on the great potential of polyphenols against different viruses that cause widespread health problems. As a result, this review focuses on the potential antiviral properties of some polyphenols and their action mechanism against various types of viruses such as coronaviruses, influenza, herpes simplex, dengue fever, and rotavirus, among others. Also, it is important to highlight the relationship between antiviral and antioxidant activity that can contribute to the protection of cells and tissues of the human body. The wide variety of action mechanisms of antiviral agents such as polyphenols against viral infections could be applied as a treatment or prevention strategy, because at the same time, antiviral polyphenols can be used to produce natural antiviral natural drugs. A recent example of an antiviral polyphenol application deals with the use of hesperidin extracted from *Citrus sinensis*. The action mechanism of hesperidin relies on its binding to the key entry or spike protein of SARS-CoV-2. Finally, the extraction, purification and recovery of polyphenols with potential antiviral activity, which are essential for virus replication and infection without side-effects, have been critically reviewed.

1. Introduction

Since ancient times, plants have played an important role for humanity, for example as food, clothing, perfumes and/or medicines (e.g., drugs in traditional medicine). Already in 1978, the World Health Organization (WHO) highlighted the need of scientific research in traditional medicine. Since then it has begun to put in value this type of medicine, as well as to investigate the efficacy of the mechanism of action and chemical bases of traditional herbal medicine for the development of new drugs, and also within the antiviral property that some plants possess (Ruwali et al., 2013; World Health Organization, 1978). Additionally, it is known that plants produce secondary metabolites such as polyphenols to protect themselves from the plethora of biotic and abiotic stresses. Biotic stress can be weeds, insect pests, fungi, and other microorganisms, whereas abiotic stresses can be physical and environmental conditions like salinity, drought, UV radiation, extreme temperatures, and toxic metals (Tuladhar et al., 2021). Polyphenols are not only involved in the defense mechanism of the plant system, but also, they have been found, for example, in the cell division, photosynthetic activity, reproduction, hormonal regulation, and nutrient mineralization mechanisms (Sharma et al., 2019). Thus, for instance, coumarins and tannins reduce stress on plants by repelling herbivores (Lattanzio, 2013).

Infections caused by viruses in humans are a critical and vitally important issue, as has been demonstrated during the last year with the 2019-nCovid caused by SARS-CoV-2 (severe acute respiratory syndrome corona virus-2) (Gorbalenya et al., 2020), in particular to safeguard the health of the population and mitigate its impact on economic and social vectors. Therefore, antiviral agents (e.g., vaccines containing specific virus, or specific antibody with protective therapeutic effect, or plants with antiviral activity) are reported to fight viral diseases, and some cases have been eradicated such as: i) smallpox, poliomyelitis (>99%); and ii) endemic measles, rubella and congenital rubella syndrome practically eliminated from America since 2010, thanks to vaccination (Plotkin et al., 2012). But although im-

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munisation and drug development have been progressing for decades, this has not been enough, as many viruses do not have preventive vaccines and, worse still, traditional antiviral treatments such as drugs with unnatural components (e.g., acyclovir for herpes) may lead to the generation of viral mutants (Lin et al., 2014).

Besides, some drugs used to combat viral diseases can cause human health hazards due to their viral resistance or, in some cases, low efficiency. In addition, viruses are made up of DNA or RNA enclosed in protein capsules (Kamboj et al., 2012), which can invade human body cells and use components from those cells for their replication. This process often damages or destroys infected cells, causing a viral disease (Rouse and Sehrawat, 2010).

On this basis, it is necessary to find alternatives to the traditional treatments for viral diseases (El-Toumy et al., 2018). Recently, the use of bioactive compounds such as polyphenols has been proposed, taking into account their potential health benefits. These substances can be found in vegetables and fruits and can also be recovered from secondary sources, such as agri-food residues (Montenegro-Landívar et al., 2021; Tapia-Quirós et al., 2020). Scientific publications have detailed more than 500 different polyphenols in more than 400 food components (Galanakis, 2018). Additionally, based on epidemiological research and associated meta-analyses, the long-term consumption of diets rich in polyphenols from plants are considered as tools that could offer protection against for example to cardiovascular diseases, neurodegenerative diseases, diabetes development, osteoporosis, and cancers development among others (Pandey and Rizvi, 2009). Therefore, polyphenols are widely promoted to be used as functional foods or in drugs preparations accepted for human consumption around the world (Cheynier, 2012; Shahidi and Ambigaipalan, 2015; Cory et al., 2018).

Recently, Russo et al. (2020), have proposed that alternative treatments to antiviral drugs may also represent a valid approach for the 2019-nCovid disease. It is also stressed that polyphenols, specifically flavonoids, can act satisfactorily in various stages of the coronavirus entry and replication stages. Another example is catechin epigallocatechin-3-gallate (EGCG), present in green tea leaves, which inhibits replication of DNA viruses such as herpes simplex (oral dose of 800 mg), and HIV-1 (concentration ranging from 25 to 250 μmol/L), among others (Steinmann et al., 2013). Moreover, the half-maximal inhibitory concentration (IC_{50}) of 47–73 μM of luteolin, hesperetin, and quercetin, among others flavonoids, can inhibit key proteins (PL^{pro}, $3CL^{pro}$) involved in the infectious cycle of SARS coronavirus (Nguyen et al., 2012; Soukhova et al., 2004). More examples can be found as described in the following, where a list of some types of viruses that could be inhibited by phytochemicals such as polyphenols is discussed. Of the diseases caused by harmful viruses where the use of polyphenols has been critically reviewed and shown an antiviral activity against them, kaempferol and quercetin extracted from *Broussonetia papyrifera* have shown activity against MERS-CoV and SARS-CoV-1 viruses, and hesperetin and naringenin block the replication of Sindbis virus, and these are examples which, with future developments, may be approved as alternative treatments. The main objective of this comprehensive review is to compile and evaluate the studies that have demonstrated the antiviral activity of polyphenols, the postulated mechanisms of action of polyphenols to defeat viruses as well as the synergy effect of antiviral and antioxidant properties against viral diseases. Additionally, the extraction, purification and recovery technologies to produce polyphenol from natural products and agri-food waste are also evaluated, since they could be limiting steps for the application of polyphenol molecules as an alternative against viruses on a large scale.

1.1. Therapeutic tools against viral diseases

The type of virus diseases and the specific virus considered in the review are summarized in Table 1, and includes: i) respiratory infections: influenza virus, coronavirus, rhinovirus, and syncytial virus; ii) gastrointestinal infections: rotavirus; iii) hepatic infections: hepatitis virus, Epstein-Barr virus, human cytomegalovirus, and herpes virus; iv) exanthematous infections: varicella-zoster virus; v) neurologic infections: rabies virus and poliovirus; vi) haemorrhagic fevers: dengue virus and Sindbis virus; vii) immune system infections: human immunodeficiency virus; and viii) multisystem disease: coxsackie virus.

In view of the examples described in Table 1, there are a large number of viruses, which can affect human health to different extent. For this reason, it is important to identify new therapeutic and functional strategies using natural sources through bioactive compounds and, more specifically, polyphenols. Furthermore, it is worth noting that polyphenols extracted from plants can efficiently inhibit the different stages of replication of various viruses in a dose-dependent matter.

2. The potential of phenolic acids and polyphenols as antiviral agents

Plants not only have the function of feeding human beings, but have also been used since ancient times as a source of therapeutic agents. According to Naithani et al. (2008), up to 80% of the world population uses plants as alternative medicine for various reasons such as their well-known antiviral features. This claimed activity is due to a wide variety of bioactive compounds present, such as polyphenols, proteins, and terpenoids, among others (Kamboj et al., 2012). Although, polyphenols are common components of the human diet, it has been reported that polyphenols are also toxic due to their biocidal activity at intake concentrations between 1 and 5% of the total daily diet (Galanakis, 2018). Considering the significant amounts of compounds that a person must be consumed, being approximately between 0.025 and 1 g per day (Scalbert and Williamson, 2000), and their multitude activities, it should be noted that they could play an important role in the prevention of numerous diseases, including antivirals. However, it is necessary to consider that despite many promising results obtained in vitro or animal experiments, there is still not enough convincing evidence from human studies, especially with large populations. More research is needed to better understand the value of therapeutic polyphenols, dietary polyphenols, and in the context of their ability to prevent the progression of diseases caused by viruses (Koch, 2019; Martin, 2009; Yang et al., 2020).

The focus of this review is on phenolic compounds and polyphenols, which have a common structural feature consisting of the presence of one or more hydroxyl groups attached to a benzene ring. Polyphenols can be classified into different classes based on their chemical structure, ranging from simple to highly polymerized compounds. Their fundamental physiological functions deal with the growth and reproduction of plants, as well as protection against pathogenic organisms and ultraviolet radiation. In addition, polyphenols strongly influence the organoleptic characteristics of food products, such as color and flavour (Ignat et al., 2011).

Polyphenols are often classified into four main families, namely: phenolic acids, flavonoids, stilbenes and lignans (Saurina and Sentellas, 2015). The basic chemical structure and examples of these polyphenol families are collected in Table 2.

As shown in Table 2, polyphenols have a great structural diversity as a function of the number of phenol rings that they contain and the

Table 1
Different families and type of viruses, their specific virus and the role of polyphenols as a possible alternative to treat virus.

Type of virus	Specific virus	Disease characteristics	Conventional treatment	Alternative treatment with polyphenols	Reference
Respiratory infections	Influenza virus (A, B and C)	Annually responsible for high mortality in both humans and animals worldwide	NA inhibitors and M2 protein channel blockers after infection, while vaccination is the most effective therapy	1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (IC_{50} of 2.36 μg/mL) purified from *Echinacea purpurea*, *Phyllanthus emblica* Linn inhibits virus replication	(Fox and Christenson, 2014; Liu et al., 2011; Moscona, 2008)
	Coronavirus (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the novel SARS-CoV-2)	Respiratory tract infections in humans with outbreaks around the world, especially in winter	Currently there are no specific treatments for the CoV infection and preventive vaccines are being developed	Polyphenol extract from *Echinacea purpurea* against SARS-CoV-2 provided 50% of inhibition. Kaempferol and quercetin from *Broussonetia papyrifera* against MERS-CoV and SARS-CoV effectively inhibited with an IC_{50} of 27.9 μM and 30.2 μM, respectively	(Chiow et al., 2016; Liu et al., 2020; Park et al., 2017; Signer et al., 2020)
	Rhinovirus	The main cause of the common cold, among other respiratory diseases, also producing shortness of breath in asthmatic people, acute otitis and bronchiolitis	There are no vaccines or antiviral agents for the prevention or treatment of this virus	Resveratrol showed a therapeutic approach to reduce infection when the IC_{50} was 50 μM. Gallic acid extracted (100 μg/mL) from *Woodfordia fruticose* flowers, reported 55% virus inhibition	(Choi et al., 2010; Mastromarino et al., 2015; Ruuskanen et al., 2013)
	Syncytial virus	Causes infections in infants and the elderly, causing not only acute morbidity but also recurrent breathing problems	There is no safe and effective treatment. Corticosteroids was treated children of preschool-age who had early bronchitis, but the results were not satisfactory and failed to reduce the infection or breathing problems	Resveratrol (IC_{50} 189 pg/mL) inhibits 40% virus replication and down-regulates the TIR-domain-containing adapter-inducing interferon-β (TRIF) complex, which sends signals for the activation of innate immune cells	(Beigelman et al., 2014; Tagarro et al., 2014; Xie et al., 2012)
Gastrointestinal infections	Rotavirus	Causes dehydrating gastroenteritis, especially in children under five years of age	There is a vaccine against rotavirus but annually the mortality is around 200,000 deaths worldwide. The treatment focuses on dehydration and not on the use of antiviral agents	Polyphenols (licocoumarone, glycyrin, among others) extracted from *Glycyrrhiza uralensis* root (EC_{50} 18.7-69.5 μM) can inhibit 50% virus absorption and replication after the cell's entry	(Crawford et al., 2017; Cushnie and Lamb, 2005; Kwon et al., 2010)
Hepatic infections	Hepatitis virus (A, B and C)	Cause high morbidity and mortality around the world	Anti-hepatitis virus drugs are members of nucleotides or nucleoside analogs, which inhibit the activity of polymerase or reverse transcriptase, but the prolonged use giving rise to the existence of mutant viruses	Curcumin (150 μM) inhibits hepatitis B virus	(Mouler Rechtman et al., 2010; Sukowati et al., 2016; Yugo et al., 2016)
	Epstein–Barr virus	Infects human epithelial and lymphoid cells. Infection is associated with a number of human cancers, such as Hodgkin's disease	A vaccine is not yet approved	(−)-Epigallocatechin gallate (EGCG) extracted from green tea (50 μM) blocked the EBV lytic cycle, inhibiting the transcription of immediate-early genes in a range of 40–50%	(Abba et al., 2015; Chang et al., 2003; Cohen, 2018)
	Human cytomegalovirus	Not present obvious symptoms, but infection causes morbidity and mortality in transplant recipients or patients with acquired immunodeficiency syndrome (AIDS)	Drugs such as cidofovir, valganciclovir and ganciclovir, which target viral DNA polymerase, but their side-effects include long-term toxicity, low bioavailability, plus drug resistance to the virus	Curcumin, using a low dose of 0.2 μg/mL, inhibits virus protein expression	(Ahmed, 2012; Evers et al., 2005; Lv et al., 2014)

Table 1 (*Continued*)

Type of virus	Specific virus	Disease characteristics	Conventional treatment	Alternative treatment with polyphenols	Reference
	Herpes simplex virus (HSV-1 and HSV-2)	Responsible for orolabial and genital diseases producing, in general, benign lesions but, in some cases, putting the life of patients at risk if the infections are recurrent	There is no vaccine and existing drugs (e.g., acyclovir) do not eradicate the virus infection and cause resistance to drugs	Ent-epiafzelechin-(4$\propto \rightarrow$8)-epiafzelechin extracted from *Cassia javanica* leaves (250 μM of) inhibits more than 90% of HSV-2 penetration to the host cell	(Cheng et al., 2006; Morfin and Thou, 2003; Piret and Boivin, 2011)
Exanthematous infections	Varicella-zoster virus	Causes fever and vesicular rash. Once the disease has disappeared, the virus enters into a state of latency, but it can be reactivated due to stress, causing herpes zoster and acute pain in latently infected lymph nodes	Generally, uses drugs such as acyclovir, valaciclovir, etc., which are often combined with analgesics for pain and corticosteroids for inflammation	Resveratrol (219 μM of) inhibits 100% virus replication	(Docherty et al., 2006; Johnson and Whitton, 2004)
Neurologic infections	Rabies virus	Causes an acute and fatal neurological infection in humans and mammals	Disease can be prevented by vaccination	Tannin pentagalloylglucose (PGG) (10 μM) for 24 h possess significant anti-RABV activity; PGG can reverse the expression of miR-455-5p (a microRNA whose excess production regulates host cell signalling pathways and innate immune responses)	(Fisher et al., 2018; Riedel et al., 2019; Tu et al., 2019)
	Polio virus	The virus drains into the cervical and mesenteric lymph nodes and then into the blood, causing a transient viremia	The incidence has been largely reduced especially by the use of a vaccine, but the disease is still endemic in Africa and Asia	Extract of *Avicennia marina* leaf, the IC_{50} was 145.7 μg/mL before and 314.3 μg/mL after attachment stages of virus replication, with a cytopathic effect of 50% in both stages	(Felipe et al., 2006; Racaniello, 2006; Zandi et al., 2009)
Haemorrhagic fevers	Dengue virus	Causing from a mild fever to haemorrhagic fever, nausea, joint pains, etc.	There are no effective vaccines, and the prevention options available for the control of the virus infection are very limited	Baicalein (IC_{50} was 7.14 μg/mL) potent antiviral agent against adsorption in the host and after entry viral replication, and IC_{50} of 1.55 μg/mL presents a virucidal effect	(Zandi et al., 2011, 2012)
	Sindbis virus	Cause of disease outbreaks in humans in South Africa and Northern Europe	There are no vaccines or therapeutic means	Hesperidin and naringenin with a 50% inhibitory dose (ID_{50}) of 20.5 μg/mL and 14.9 μg/mL respectively, reaching 50% for hesperidin and up to 80% for naringenin of virus replication inhibition	(Ling et al., 2019; Paredes et al., 2003)
Immune system infection	Human immunodeficiency virus (HIV-1 and HIV-2)	Spreads through certain body fluids and attacks the immune system, destroying T lymphocytes. Thus, the body loses its ability to fight infections and diseases	Since HIV was discovered, there has been no preventive vaccine for virus infection, and the applied treatment is antiretroviral therapy drugs which help control the multiplication of HIV in infected patients	Tricyclic coumarin compound from *Calophyllum brasiliense* stem bark (IC_{50} was 8.44 μM) inhibits virus replication by suppressing nuclear factor-kappa B (a protein complex that controls DNA transcription) activation	(Bhatti et al., 2016; Häggblom et al., 2016; Kudo et al., 2013; Lin et al., 2014; Sundquist and Kräusslich, 2012)
Multisystem diseases	Coxsackie virus	Causes muscle injury, paralysis and death	There is no specific treatment or vaccine available	Apigenin ((EC_{50} of 9.7 mg/L) and ursolic acid (EC_{50} of6.6 mg/L) extracted from *Ocimum basilicum* interfere with virus replication after infection	(Bedard and Semler, 2004; Chiang et al., 2005; Wong et al., 2013)

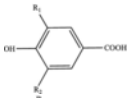
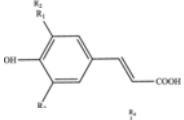
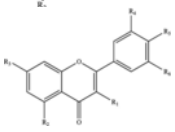
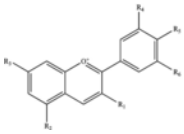
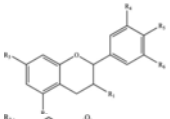
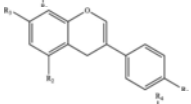
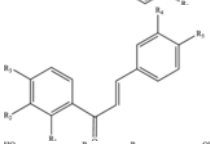
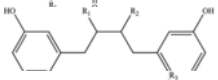
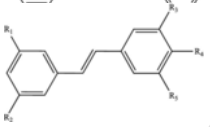
elements that bind these rings. Flavonoids are the largest and most studied group.

Phenolic acids possess a high antioxidant capacity and their medical properties, such as vasodilatory, antibacterial, antiviral, anticarcinogenic and anti-inflammatory, have been reported elsewhere (Oroian and Escriche, 2015).

An important derivation from hydroxybenzoic acids are the so-called hydrolysable tannins, which are mostly present as phenolic polymers with different molecular weights, from 500 to 3000 Da (Andronescu and Grumezescu, 2017). As their principal characteristic, tannins precipitate proteins, thus contributing to regenerate, for example, a burn tissue, besides their antimicrobial, antioxidant and antiviral properties (Haminiuk et al., 2012). Their antiviral activity against Epstein–Barr virus DNA polymerase has been demonstrated, and especially those tannins extracted from mouse-tail plant (*Phyllanthus myrtifolius*) and chamber bitter (*Phyllanthus urinaria*) (Naithani et al., 2008).

Regarding flavonoids, they represent the largest amount of polyphenols (up to 60%) consumed in the human diet (Brglez Mojzer et al., 2016). Actually, more than 9000 different flavonoids have been reported, having important benefits on human health because of their antiviral, anti-inflammatory and antidiabetic attributes (Zhang et al.,

Table 2
List of relevant polyphenol classified according to their structure (adapted from Saurina and Sentellas, 2015).

Class	Structure	Substitutions	Examples
Phenolic acids		R1: H, OH, OCH_3	Gallic acid
Hydroxybenzoic acids		R2: H, OH, OCH_3	Vanillic acid
			Procyanidin B1
			Theogallin
Hydroxycinnamic acids		R1: H, OH, OCH_3	Caffeic acid
		R2: H, OH, OCH_3	Ferulic acid
			p-Coumaric acid
			Rosmarinic acid
Flavonoids		R1: H, OH	Hesperidin
Flavonols		R2: H, OH	Naringenin
Flavones		R3: H, OH	Quercetin
Flavanones		R4: H, OH	Kaempferol
		R5: OH, OCH_3	Luteolin
		R6: H, OH	
Anthocyanidins		R1: H, OH	Cyanidin
		R2: OH, OCH_3	Pelargonidin
		R3: OH	
		R4: H, OH	
		R5: OH	
		R6: H, OH	
Catechins		R1-R3: OH	Catechin
		R4: H, OH	Epicatechin
		R5: OH	Epigallocatechin
		R6: H, OH	
Isoflavones		R1: OH	Genistein
		R2-R3: H, OH	Daidzein
Chalcones		R1-R5: H, OH	Xanthohumol
			Phloretin
			Isosalipurpurin
Lignans		R1-R2: H, OH	Enterodiol
			Matairesinol
Stilbenes		R1-R4: H, OH, OCH_3	Resveratrol
		R5: H, OH	Piceatannol

2015; Krych and Gebicka, 2013; Tian et al., 2013; Ragab et al., 2014). Flavonoids have been studied against the type-1 and type-2 herpes simplex virus, and against the human immunodeficiency virus (HIV-1 and HIV-2) (Naithani et al., 2008).

Finally, stilbenes (including curcuminoids) and lignans have been extensively studied because of their antioxidant properties, but their antiviral activity is not far behind. These compounds and their derivates have been studied against viruses such as herpes simplex (type-1 and type-2), HIV, influenza, and human papilloma, among others (Naithani et al., 2008; Abba et al., 2015).

A list of polyphenols with antiviral activity, the type of virus against which they act, and their plant source is collected in Table 3.

As shown in Table 3, polyphenols with antiviral activity such as quercetin, rutin, hesperidin, apigenin, catechin, and morin are present in abundance in plants like fruits (e.g., berries, citrus fruits, tropical fruits), popular beverages (e.g., green tea, coffee), vegetables (e.g., spinach, beans, onions, olives), spices and herbs (e.g., turmeric, rosemary, ginger), which are consumed in the daily human diet (Brglez Mojzer et al., 2016). Currently, the antiviral activity of various polyphenols makes their study more attractive; for example, 3 mg/kg body weight of curcumin, extracted and purified from turmeric, is sufficient to inhibit HIV (Praditya et al., 2019; Barthelemy et al., 1998; Haslberger et al., 2020).

2.1. Polyphenol recovery from secondary sources

Phenolic compounds can also be obtained from by-products of plant processing, being cheap and easily available to recover, which follow a circular economy strategy (Tapia-Quirós et al., 2020; Montenegro-Landívar et al., 2021). In addition, the growing interest in polyphenols recovery has led to the study of different technologies that can allow their extraction without losing their antiviral properties (Dzah et al., 2020). Successful cases of extraction and recovery of polyphenols with antiviral activity is summarized in Table 4.

Table 4 lists not only the application of polyphenols extracted from different plant sources against numerous target viruses, but also the different extraction techniques integrated, being maceration being the most used. Most of the trials were carried out on a pilot scale.

The polyphenols extraction from plants or from their processing waste streams can be achieved by conventional (e.g., mechanical stirring) and enhanced (e.g., ultrasound and microwave assisted) solid-liquid extractions or by combination of both extraction approaches by means of organic and aqueous/organic solvents. For their subsequent

Table 3
Summary of relevant polyphenols present in plants with antiviral activity according to the reviewed publications.

Plant source	Polyphenol	Type of virus	Reference
Berries, tea, almond, beans, tomato, *Ficus carica* L., capers, caraway, cloves, cumin, Cambuci	Kaempferol	Coronavirus, rotavirus, human cytomegalovirus, HSV-1 and HSV-2, coxsackie B virus	(Naithani et al., 2008; Kamboj et al., 2012; Russo et al., 2020; Watson et al., 2013; Haminiuk et al., 2012)
Propolis, *Oroxylum indicum*	Chrysin	Coronavirus, rotavirus, human cytomegalovirus, HSV-1 and HSV-2, coxsackie B virus	(Cheng and Wong, 1996; Kumar and Pandey, 2013; Cushnie and Lamb, 2005)
Euphorbia cooperi, *Morus alba*, *Rhus succedanea*	Catechin	HIV, HSV-1	(Kamboj et al., 2012; Cushnie and Lamb, 2005; El-Toumy et al., 2018)
Citrus spp., cocoa, fish mint (*H. cordata*), *Spondias mombin*, *Spondias tuberosa*	Quercetin	Rabies virus, poliovirus, syncytial virus, HSV-2, respiratory syncytial virus, dengue virus, coronavirus	(Suárez et al., 2010; Silva et al., 2011; Zandi et al., 2011; El-Toumy et al., 2018; Chiow et al., 2016)
Betula pendula, apple	Quercitrin	Rabies virus, HSV-1, influenza virus	(Kumar and Pandey, 2013; Suárez et al., 2010)
Spondias spp., *Pavetta owariensis* (bark)	Rutin	Rabies virus, influenza virus, dengue virus	(Kamboj et al., 2012; Cushnie and Lamb, 2005)
Citrus spp., peppermint, grapefruit	Hesperidin	Influenza virus, HSV, poliovirus, syncytial virus, SARS-CoV-2	(Mhatre et al., 2020; Bellavite and Donzelli, 2020)
Chamomile, parsley, oregano, thyme, grapefruit, orange, onion, mango	Apigenin	HSV-1, HIV	(Kumar and Pandey, 2013; Kamboj et al., 2012)
Citrus spp., tomato, aromatic plants	Naringin	Respiratory syncytial virus	(Kumar and Pandey, 2013)
Broadleaf plantain (*Plantago major*), papaya, peach, avocado	Caffeic acid	HIV, HSV	(Pommier et al., 2005; Sytar et al., 2021)
Broccoli, rosemary, pistachio, lentils, olive, artichoke, lemon, *Aloe vera*	Luteolin	HSV-1 and HSV-2	(Naithani et al., 2008; Lopez-Lazaro, 2008)
Berries, pomegranate, walnuts, pecans	Ellagic acid	Dengue virus, hepatitis A and B	(Kang et al., 2006; Kamboj et al., 2012)
Grape, berries, peanuts	Resveratrol	Influenza A, hepatitis C virus, respiratory syncytial virus, varicella-zoster virus, Epstein–Barr virus, HSV, HIV	(Docherty et al., 2006; Mastromarino et al., 2015)

purification implies a preliminary stage of clean-up and concentration by using sorption on resins, or pressure-driven membrane processes such as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO) followed by a final purification by using extraction chromatography (Bottino et al., 2020; Charcosset, 2016).

As mentioned, the commonest technique for polyphenols extraction is maceration (e.g., solid-liquid extraction). For example, Edziri et al. (2012) used maceration for polyphenol extraction from *Marrubium deserti*. The dried product (250 g) was extracted with methanol, butanol, chloroform and ethyl acetate (using a feed to solvent ratio of 1:10) for an extraction time of five days. Results from antiviral activity tests concluded that the extracts with methanol and ethyl acetate showed significant antiviral activity against coxsackie B3 virus with IC_{50} of 100 and 135 μg/mL, respectively.

Magnetic agitation at 20 °C has been applied to recover active components from apple pomace (10 g) using 100 mL of 70% acetone and 80% methanol in darkness. The results showed that acetonic and methanolic extracts could inhibit the replication of HSV-1 and HSV-2 by more than 50% (Suárez et al., 2010).

The purification of plant extracts is, in general, a complex process and no single method is complete enough. It requires a combination and integration of them to achieve the highest separation and purification factors. A successful example is the study by Zahoor et al. (2020), who compared the separation efficiency of quercetin extracted from *Rubus fruticosus* by using RO and NF membranes. Quercetin is used against rabies virus, poliovirus, syncytial virus, and HSV-2, among other viruses (Suárez et al., 2010; Silva et al., 2011; Zandi et al., 2011; El-Toumy et al., 2018; Chiow et al., 2016). The results obtained indicated that the RO membrane accomplished a quantitative recovery (e.g., >99%) of the drainage pipe, while NF membranes achieved a 95% recovery. The study shown that the cost of use the RO membranes is higher, due to the higher energy consumption, and the use a NF membrane stage followed by a sorption stage of the remaining 5% of the permeate stream by using magnetic carbon nanocomposite.

It should be noted that the phenolic compounds recovered from extracts, such as kaempferol, luteolin, chrysin, gallic acid, ferulic acid, catechin, anthocyanins between others have been used as a treatment or for prevention against virus infection (Singh et al., 2020; Kumar and Goel, 2019; Watson et al., 2013; Marín et al., 2015).

2.2. Economic prospects of polyphenol recovery

Taking into account the different antiviral applications of polyphenol extracts, as well as the need to investigate innovative extraction and purification procedures, it is interesting to mention some examples of the economic evaluation of the recovery of polyphenols, which is also applicable to antiviral polyphenols.

The manufacturing cost (COM), expressed as €/kg per year, of the polyphenols extraction from raw material could be estimated using the methodology described by Turton et al. (2009), where five main costs must be taken into account: (i) fixed capital investment (FCI),

Table 4
Applications of extracted polyphenols from different plant sources to treat several target viruses.

Antiviral polyphenol	Plant source	Target virus	Extraction technique	Purification technique	Study effectiveness against virus	Results	Scaling-up	Reference
1,2,3,4,6-Penta-O-galloyl-ß-D-glucose (PGG)	Pomegranate	Influenza A (H1N1)	Maceration	Sephadex LH-20 column	EC_{50} 2.36 ± 0.29 μg/mL of PGG 5 or 8 h upon infection	Significant inhibition virus release	Lab scale	(Liu et al., 2011)
Extract rich in polyphenols	*Magnolia officinalis* bark	Influenza A (H1N1)	PLE	–	In vivo oral administration (10 and 20 mg/kg) for 5 days	Infected mice reduce the production of nitric oxide, pro-inflammatory cytokines, TNF-α and IL-6	Pilot scale	(Wu et al., 2011)
Isoquercetin (quercetin glucoside form)	*Hypericum perforatum*, *Equisetum arvense L.*	Influenza A (H1N1)	Maceration	–	In vivo administrated intraperitoneal	Reduce virus titres and pathological changes in lungs of mice infected with influenza A (H1N1) by up to 20-fold at 1:500 (*Equisetum arvense L.*) or 1:1000 dilutions (*Hypericum perforatum*) at 24 h post-inoculation	Pilot scale	(Kim et al., 2010)
Baicalein	*Scutellaria baicalensis* root	Influenza H1N1	Maceration	–	In vivo oral administration	Infected mice showed significant therapeutic activities, including death prevention and lung virus titre reduction	Pilot scale	(Xu et al., 2010)
Quercetin, kaempferol, myricetin, quercetin-3-*O*-galactoside, morin, apigenin, catechin, epicatechin, caffeic acid and rimantadine	*Geranium sanguineum* aerial roots	Influenza (H3N2)	Maceration	–	Administered in aerosol way (dose 5.4 mg/mL)	Around 70% was the protective index and the survival time was in a range of 2.9–4.9 days, the animal lung infectious virus titre was reduced in comparison with control	Pilot scale	(Serkedjieva et al., 2008)
Epigallocatechingallate (EGCG), epigallocatechin (EGC), epicatechingallate (ECG), epicatechin (EC) and catechin gallate	Tea	Influenza	Maceration	–	76 adult persons around 65 years old gargling 200 mg/mL 3 times daily for 3 months	The catechin-treated group have lower incidence of influenza infection than the control group	Pilot scale	(Yamada et al., 2006)

(ii) cost of operating labour (COL), (iii) cost of utilities (CUT), (iv) cost of waste treatment (CWT), and (v) cost of raw material (CRM). Following this methodology, Vieira et al. (2013, 2017) compared the COM of extraction of jussara pulp (*Euterpe edulis* Martius) with strong antioxidant activity by UAE and agitated bed extraction (ABE) at lab scale. The UAE extracts presented a higher cost (75.2–137.2 €/kg) than the ABE extracts (72.5–139 €/kg). It was reported that the ABE and UAE extracts contained polyphenols such as kaempferol, luteolin, apigenin, quercetin and rutin, which may have medical applications (e.g., antivirals) for human health; and anthocyanidins as natural pigments foe feed applications (Favaro et al., 2018; Vieira et al., 2017). Moreover, Osorio-Tobón et al. (2014) also used the COM methodology to evaluate the extraction process of curcumin from turmeric (*Curcuma longa* Linneo), which possesses a remarkable antiviral effect against dengue virus (Ichsyani et al., 2017). When advanced solid-liquid extractions techniques were evaluated, PLE, Soxhlet extraction and low-pressure solvent extraction (LPSE), COM values of f 79, 204 and 161 €/kg, respectively were estimated. The results showed that the PLE extraction technique was less expensive due to the short extraction time required (e.g., 30 min) compared with 6 h for Soxhlet and 3 h for LPSE. However, the extraction yields of the three techniques were similar (PLE 11 ± 1, Soxhlet 12 ± 1 and LPSE 12 ± 1).

On the other hand, Ioannou-Ttofa et al. (2017) determined that the total cost of the treatment of olive mill waste water through an integrated process using UF and NF membranes (UFZW-10/NF270) was 9.94 €/m^3. High-added value polyphenols present in it like hydroxytyrosol can be purified, the cost can range from 14,900 to 20,900 €/kg.

Besides, it is worth noting that the market value of 10 mg of kaempferol (≥90% purity) is 113 €, 10 mg of luteolin (≥98%) is 169 €, 10 mg of apigenin (≥97%) is 92.20 €, 10 g of quercetin (≥95%) is 44.10 €, 10 g of rutin (≥94%) is 23.60 € and 10 mg of hydroxytyrosol is 191 € (≥90%).

2.3. Stability, reactivity, synergism and bioavailability of polyphenols

Technically, polyphenols are extracted, purified and concentrated from plants using different techniques as described above, which can be processed into tablets or capsules for human consumption. However, polyphenols are unstable, prone to degrade and/or react with some elements (e.g., oxygen and metal ions during their processing and storage stages), resulting in changing structures and decreasing

activities (e.g., antiviral activity) (Galanakis, 2018). Therefore, the stability as well as their reactivity, synergism and bioavailability of polyphenols are the main aspects that must be taken into account in the recovery, processing, storage and consumption of phenolic compounds for their market applications.

2.3.1. Stability

Instability generally due to many polyphenols are sensitive to chemical, enzymatic and physical treatments, which are used in food processing. Chemical and enzymatic instability leads to changes such as oxidation or polymerization, among others, causing alterations on their nutritional and physical-chemical attributes. Physical instability leads to changes like phase separation, flocculation, etc. that can also alter their attributes (Joye and McClements, 2014; Zhang et al., 2020).

2.3.2. Reactivity

Another factor that influences polyphenols is their reactivity, as they can be enzymatically degraded and polymerized during food processing stages. One of the most notable enzymatic reactions is on color, taste and nutritional value of polyphenols, which can even cause significant economic problems due to their impact on quality and shelf life of the products (Galanakis, 2018).

2.3.3. Synergism

The synergism of polyphenols in plant extracts means that a combination of two or more of compounds creates a higher biological activity than when the extracts are analyzed relative to individual polyphenols isolated from the same extracts (Yao et al., 2012; Zhang et al., 2020). However, the commercial application of polyphenols is currently limited due to instability when exposed to light, heat or oxygen as well as low bioavailability. A solution of the limitations mentioned, it could be the encapsulation (Zhang et al., 2020). Long et al. (2015) showed that bioactive food compounds can produce synergistic effects, as they have been reported in traditional Chinese medicine research. Therefore, the synergism between polyphenols must be taken into account for the development of functional foods and thus promote human well-being and prevent diseases such as viral ones.

2.3.4. Bioavailability

Bioavailability plays an important role in terms of the biological properties of polyphenols, which makes it possible to understand the proportion of their absorption, digestion and metabolism after their entry into the circulatory system (Carbonell-Capella et al., 2014). Several epidemiological and experimental studies describe the protective role of polyphenols in diseases such as viral diseases, diabetes, inflammation, among others (Kumar and Goel, 2019). Scalbert and Williamson (2000) reported few human bioavailability studies showing that the amounts of intact polyphenols in urine vary from one to another polyphenols. For example, for quercetin glycoside the percentage found in excretion urine was between 0.3 and 1.4%, while in the case of hesperidin, it was 24.4%. Similar variations were also observed for naringin consumed with grapefruit juice depending on the individual (5 to 57%).

Hong et al. (2014) and Liang et al. (2017) demonstrated that EGCG loading in nanoparticles constructed with zein a protein as zein or with a polysaccharide as chitosan, improved the stability of said polyphenols at the gastrointestinal level. Another study by Xue et al. (2014) using glycosylated casein nanoparticles to encapsulate EGC demonstrated the improvement of its physical stability during storage. Xue et al. (2018) encapsulated curcumin in zein-caseinate nanoparticles, and reported improved stability against UV radiation and heat treatments.

On the other hand, there has also been an interest in encapsulating combinations of polyphenols and taking advantage of their synergistic effects. For example, curcumin and resveratrol have been encapsulated within hyaluronic-coated lipid droplets, as they have similar mechanisms of action to inhibit tumor cell growth and antioxidant and antiviral effects (Nasr, 2016). Encapsulated polyphenols have been shown to have better chemical stability that non-encapsulated ones. However, after encapsulation no improvement in the bioavailability of polyphenols has been observed, as polyphenols can become indigestible. Therefore, the most appropriate administration system for the polyphenols and the food matrix used should be thoroughly evaluated case by case (Dueik and Bouchon, 2016).

3. Antiviral activity of polyphenols

The antiviral activity of different polyphenols has the target of interacting directly with viral particles, but this binding will depend on the nature of the virus (DNA or RNA virus) (Sundararajan et al., 2010; Palamara et al., 2005; Liu et al., 2011). Another characteristic of antiviral polyphenols is that they can exert the activity during intracellular replication, which may be attributed to antioxidant features of phenolic groups, thus inhibiting the oxidation of cells by the replication of some viruses (Sundararajan et al., 2010; Fraternale et al., 2009).

Many natural polyphenols have provided research results and are becoming an important target in the development of some drugs to combat viruses, thanks to their wide availability, inexpensive production and, above all, their low side-effects (Kumar and Goel, 2019; El-Toumy et al., 2018). This is the case with the virus that is currently attacking the entire world, the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), which causes the 2019-nCoV disease transmitted person-to-person (Kampf et al., 2020).

As of June 2021, a total of nearly 171 million confirmed cases have been reported, including almost 4 million deaths worldwide since the start of the outbreak (World Health Organization, 2020). Due to the high infectivity and mortality rate of SARS-CoV-2, there is an opportunity to use the great amount of information on plants used in the Traditional Chinese Medicine (TCM) to be used to treat symptoms related to SARS, due to the homology of SARS-CoV and SARS-CoV-2, considering that natural polyphenols could inhibit SARS-CoV-2 (Mehany et al., 2021). According to Wang et al. (2020) and Chojnacka et al. (2020), the entry of SARS-CoV-2 into the host cells (lung epithelium) is facilitated by a trimeric glycoprotein called the spike protein (protein S), located in the capsid of the virus (outer envelope). SARS-CoV-2 uses angiotensin converting protein II (ACE2) as a receptor for binding to host cells. The protein S is hydrolysed by endosomal proteases, such as cathepsin or transmembrane cellular serine protease 2 (TMPRSS2), which results in membrane fusion. After the virus enters the host cell, it produces new RNA and the proteins that form its envelope. The binding of SARS-CoV-2 to the receptor ACE2 may depend on several factors, such as variants in the virus protein S that promote the efficiency of their interaction. In the replication and transcription, the main protease $3CL^{pro}$ and papain-like protease (PL^{pro}) are involved. The therapeutic targets to protect the human body from the entry, replication and transcription of the SARS-CoV-2 virus are the receptor with the proteases cutting spike protein and the proteases. Polyphenols with antiviral activity (e.g., flavonoids such as kaempferol, quercetin, and naringenin, see Table 3) have been developed as protease inhibitors, helping to stop virus infection (e.g., HIV, MERS and SARS) (Paraiso et al.,

2020). Current studies show that some extracted polyphenols have antiviral activity, specifically as protease inhibitors. Park et al. (2016) used 95% ethanol to extract chalcones from *Angelica keiskei* that showed inhibition of protease $3CL^{pro}$ as well as non-competitive inhibition of protease PL^{pro} of SARS-CoV with IC_{50} values of 11.4 and 1.2 μM, respectively. Also Park et al. (2017) extracted polyphenols with ethanol from *Broussonetia papyrifera* with potential anti-coronaviral agents, which inhibit 100% PL^{pro} (the IC_{50} was 3.7 μM) protease. Recent studies such as Yudi Utomo and Meiyanto (2020) reported that hesperidin and naringenin, among other citrus flavonoids, and polyphenols from *Curcuma* spp., such as curcumin, bind strongly to the $3CL^{pro}$ substrate, the binding domain of SARS-CoV-2, while interacting with the receptor ACE2 and protein S. Khalifa et al. (2020a) demonstrated that anthocyanidins, such as cyanodelphine, phacelianin, techofilin and gentiodelphin, authentically interact with the receptor binding site of SARS-CoV-2-$3CL^{pro}$. Khalifa et al. (2020b) found that pedunculagin, castalin and tercatain, which are tannins, strongly interact with the SARS-CoV-2-$3CL^{pro}$ receptor binding site. Other polyphenols such as sinigrin, with IC_{50} of 217 μM, and hesperidin, with IC_{50} of 8.3 μM, contained in the water extract of the root of *Isatis indigotica*, have also been shown to be anti-SARS-CoV-2-$3CL^{pro}$ (Xu et al., 2020). These studies triggered that some polyphenols could be used as effective and above all natural anti-2019-nCovid components. Even, the Chinese Health Commission officially confirmed that natural medicine (TCM) should be used in combination with conventional medicine for the treatment of 2019-nCovid patients, and currently experimental research is focused on the therapeutic potential of polyphenols against SARS-CoV-2 (Yang et al., 2020). Table 5 collects a summary of the antiviral activities of recent studies of natural polyphenols and their mechanism of action against SARS-CoV-2.

Although Table 5 present more in silico experiments that predict promising results, more in vitro and in vivo studies are needed to evaluate the mechanism of action of polyphenols against SARS-CoV-2. Most of the studies were carried out in silico, current technology to predict drug behavior, accelerating the detection rate, since it allows screening many drugs and reduction of the cost of laboratory work, limiting clinical trials to the best candidates.

Recently has been discovered that hesperidin (which is a flavonoid) easily binds to key proteins of the SARS-CoV-2, due to its physicochemical structure (see Table 2) (Adem et al., 2020; Chen et al., 2020; Das et al., 2021; Joshi et al., 2020; Wu et al., 2020; Yudi Utomo and Meiyanto, 2020). What authors investigated if hesperidin is able to bind with a low binding energy. The lower energy required, the stronger and more specific the binding will be in therapeutic terms. Wu et al. (2020) tested hesperidin as a potent antiviral agent. The binding of hesperidin to the spike protein was effective in superimposing the ACE2-receptor binding domain (RBD) on the hesperidin-RBD complex, where a clear overlap of hesperidin with the ACE2 interface was observed. Accordingly, it was concluded that hesperidin can interrupt the ACE2 with RBD. Another low-energy binding site for hesperidin against SARS-CoV-2 is the main protease. This enzyme is called $3CL^{pro}$ or M^{pro} and is the target of many chemical antiviral drugs. Das et al. (2021) studied the molecular coupling of the interaction between hesperidin and M^{pro}. The binding energy of hesperidin with hydrogen bonds to various amino acids (e.g., THR24, THR45, HIS4, SER46, etc.) was estimated as −37.7 kJ/mol. Hesperidin binds. Finally Joshi et al. (2020) identified that hesperidin binds strongly to the main SARS-CoV-2 protease, and also to the ACE2-receptor.

About in vitro analysis, Suru et al. (2021) using in silico and in vitro *studies* confirmed that pomegranate peel extract and its main polyphenols, such as punicalin and punicalagin, have a great capacity to attenuate the binding of the SARS-CoV-2 glycoprotein S to the ACE2 receptor. The most pronounced in vitro activity was observed in pomegranate peel extract, suggesting a possible synergistic effect of polyphenols, allowing their possible therapeutic application for 2019-nCovid.

On the other hand, there are few in vivo studies investigating the antiviral effect of polyphenols against this novel virus. Deng et al. (2020), studied Pudilan Xiaoyan Oral Liquid (EC_{50} of 1.078 mg/mL), a traditional Chinese medicine containing four herbs: Indigowoad root (*Isatis indigotica*), Bunge Corydalis (*Corydalis bungeana*), Mongolian Dandelion (*Taraxacum mongolicum*), Scutellaria Amoena (*Scutellaria baicalensis*) as well as more than 180 compounds (e.g., polyphenols such as chrysin, apigenin, rutin among others), which exhibited potent anti-SARS-CoV-2 activity in infected hACE2 mice. In another study, Schettig et al. (2020) reported that a nebulized formulation of quercetin (20 mg/mL) and *N*-acetylcysteine (100 mg/mL) greatly alleviated the respiratory symptoms of SARS-CoV-2 in a patient treated with hydroxychloroquine and antibiotics. This demonstrates the importance of conducting further clinical (in vivo) studies to evaluate the potential of polyphenols as an adjuvant or primary therapy for 2019-nCovid.

If polyphenols are analyzed in depth as traditional anti-2019-nCovid therapeutics on humans, they could be innovative and effective, or even against other lethal viral diseases. The use of medicinal

Table 5
Selected polyphenols and their role against SARS-CoV-2.

Polyphenol	Source	Mechanism of action	Analysis study	Reference
Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechingallate, zingerol, gingerol, and allicin	Medicinal plants	Block the enzymatic activity of SARS-CoV-$3CL^{pro}$	In silico	(Khaerunnisa et al., 2020)
Malvidin, peonidin, petunidin, pelargonidin, cyanidin and malvidin	*Pimpinella anisum* L.	Binding affinities to 3C-like protease of SARS-CoV-2 (virus replication)	In silico	(Hasan et al., 2020)
Hesperetin, myricetin, caflanone, linebacker	Medicinal plants	High affinity to protein S, helicase and protease sites on the CE2 receptor (in silico analysis); in vitro analysis shows potential caflanone to inhibit virus entry	In silico and in vitro	(Ngwa et al., 2020)
Baicalein and baicalin	*Scutellaria baicalensis* and *Oroxylum indicum*	Down-regulators of the TMPRSS-2 expression. Baicalein (IC_{50} of 0.94 μM) and baicalin (6.41 μM) promising results to $3Cl^{pro}$	In silico and in vitro	(Da Silva Antonio et al., 2020)
Polyphenol extract	*Echinacea purpurea*	Virus inactivated upon treatment with 50 μg/mL	In vitro	(Signer et al., 2020)

plants containing antiviral polyphenols, still has some risks and needs massive and additional experiments.

3.1. Antiviral mechanism

The mechanism of polyphenols deals with the prevention of the entry of the virus into the host cell. This was the case of the proanthocyanidins extracted from *Rumex acetosa*, which inhibited the entry of the influenza type A virus in its first critical phase (Daglia, 2012). Fig. 1 shows the scheme of the target sites of the antiviral mechanism of some polyphenols (e.g., quercetin, morin, chrysin).

The general interest in polyphenols as antiviral agents is increasing because of the great advantages of using nature-derived compounds with almost no side-effects on human health (Naithani et al., 2008). Several studies have been done for discovering the antiviral mechanism of different polyphenols, Table 6 gives an overview of some of them.

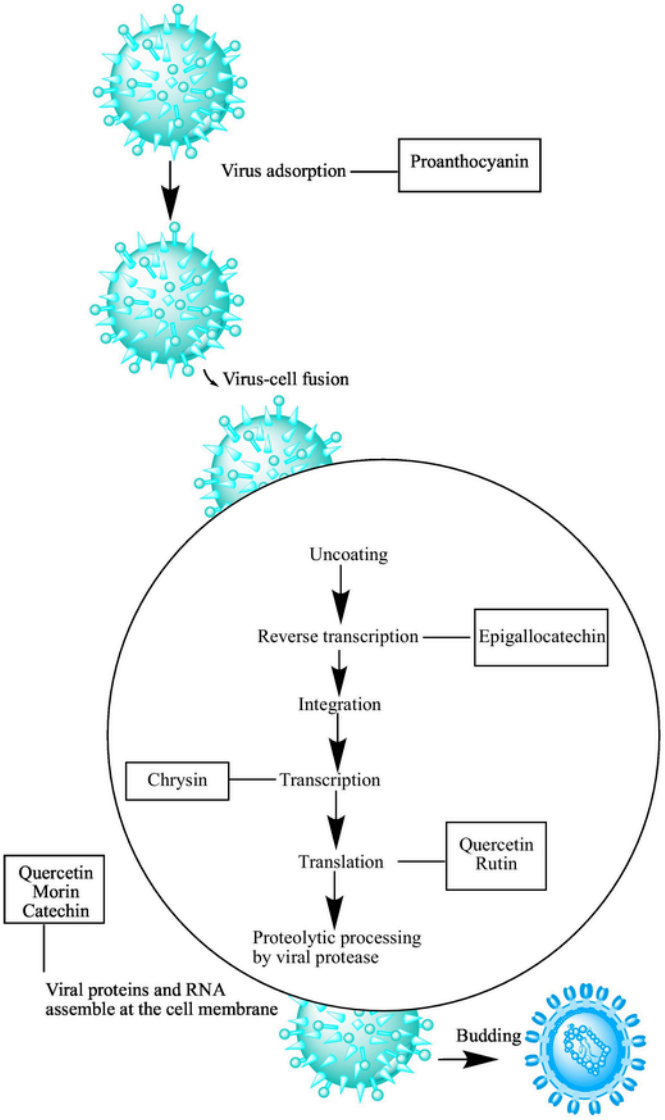


Fig. 1. Virus replication and polyphenol targets (adapted from Pommier et al., 2005; Kamboj et al., 2012).

Table 6
Examples of antiviral mechanism of polyphenols (adapted from Naithani et al., 2008; Haslberger et al., 2020).

Antiviral polyphenol	Plant source	Study	Virus type	Main mechanism
4′,5-Dihydroxy 3,3′,7-trimethoxy flavone	*Agastache rugosa* (Kuntze)	Effect on the replication virus	Rhinovirus coxsackie virus	Replication inhibition, selective inhibition of viral RNA synthesis in the cell culture
Quercetin Luteolin	*Achyrocline satureioides*	Effect on the viral replication cycle of HSV-1	HSV-1	Interferes with the events occurring between the third and ninth hour of HSV-1 replication cycle, which includes transcription and translation of viral proteins
Salvin	*Salvia officinalis*	Viral inhibitory before absorption stage	HSV-1, HIV, SARS-CoV	Efficacy before absorption stage, but not in the replication stage
Morin Coumarin Quercetin	*Rhus succedanea*, *Garcinia multiflora*, *Alnus firma*	Effect on viral replication	HIV	Blockage of RNA synthesis, exhibited HIV-inhibitory activity

As shown in Table 6, the given agents may have different mechanisms of action, such as inhibiting the entry of the virus, an effect on replication, etc. (Haslberger et al., 2020). New trends in biotechnology and medicine, as well as new processing technologies, could help to optimise the solubility, administration and therapeutic activities to prevent infection by viruses (Patra et al., 2018; Thomford et al., 2018; Lin et al., 2014).

3.2. Relationship between antiviral activity and antioxidant property

The study of the relationship between antiviral and antioxidant activities has not been explored in depth. Only a few studies report a comparative evaluation. It is worth mentioning that a high formation of free radicals leads to an imbalance in the oxidative metabolism at the mitochondrial level and, as a result, the vitality of the cells of each tissue is affected (Delgado-Roche and Mesta, 2020). This imbalance can be caused by various viruses (e.g., SARS-CoV-2, HIV, influenza virus) and leads to oxidative stress and helps the virus life cycle and eventually causes cell death (Bellavite and Donzelli, 2020).

Viral infection disrupts the defensive antioxidant mechanism of the human body, bringing inflammation and oxidative damage. Experimental animal models have achieved high levels of reactive oxygen species (ROS) and an alteration of innate antioxidant defenses during, for example, a SARS-CoV infection (van den Brand et al., 2014).

Therefore, the use of polyphenols with antiviral and antioxidant activities could be an alternative to prevent the onset of infection or development of viral disease. For example, Lin et al. (2002) reported that HSV-2 infection increases the amount of free radicals and consequently causes immune response pathology, so they used an ethyl acetate extract from *Euphorbia thymifolia* (with antiviral and antioxi-

dant activities, the IC_{50} was 7.72 ± 0.15 μg/mL) to inhibit HSV-2 growth in the kidney cell line.

As mentioned, many of the pathological effects of the viruses are not only directly related to viral replication, but also to the host response to infection (e.g., inflammation, oxidative stress, etc.) (Mateos-Martín et al., 2014; Bellavite and Donzelli, 2020). Therefore, the combination of antiviral therapy with the antioxidant properties could help favourably to combat the virus infection, reducing toxicity and preventing antiviral resistance.

4. Conclusions

Keeping in mind that diseases caused by viruses remain among the leading causes of morbidity and mortality, in both developed and developing countries, despite having conventional medicine, it is of interest to looking for alternative treatments more biocompatible for humans. As an example of alternative treatments, polyphenols are interesting and promising molecules that could be applied in the pharmaceutical sector. Polyphenols are secondary metabolites from plants which can also be extracted from agri-food residues. The bioactivities of polyphenols, like antioxidant capacity, as well as their mechanisms, such as forming stable radicals, delay and/or prevent oxidative stress-induced cellular damage and disease, are well defined and studied. However, in this comprehensive review, it has specifically shown the potential role of polyphenols with potential targets, such as antiviral activity, in the prevention of diseases caused by viruses. The state of the art indicates that there is not a single mechanism of action of polyphenols. Indeed, the antiviral mechanism of these compounds can be by antioxidant activities, viral entry or inhibition of viral reproduction, DNA inhibition between others.

Additionally, due to the complex polyphenol structure, new extraction, purification, formulation and processing technologies could help to improve the stability and bioavailability of antiviral polyphenols, as well as the administration protocols and the therapeutic effects as antiviral treatments. Thus, the use of plant extracts, as polyphenols, is postulated as useful for health, due to their synergistic effects, such as antioxidant, antiviral, anti-inflammatory, among others that must be considered and studied intensively. Therefore, future and more comprehensive studies of the antiviral activity of polyphenols against the SARS-CoV-2 coronavirus could provide an additional strategy, for example as a curative treatment in vaccines, to combat this pandemic that is causing the deadly disease 2019-nCovid.

Uncited reference

Cheah et al., 2010

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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